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Vitamin E intake from natural sources and head and neck cancer risk: a pooled analysis in the International Head and Neck Cancer Epidemiology consortium

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Background: Evidence for the possible effect of vitamin E on head and neck cancers (HNCs) is limited.

Methods: We used individual-level pooled data from 10 case–control studies (5959 cases and 12 248 controls) participating in the International Head and Neck Cancer Epidemiology (INHANCE) consortium to assess the association between vitamin E intake from natural sources and cancer of the oral cavity/pharynx and larynx. Adjusted odds ratios (ORs) and 95% confidence

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intervals (CIs) were estimated using unconditional logistic regression models applied to quintile categories of nonalcohol energy-adjusted vitamin E intake.

Results: Intake of vitamin E was inversely related to oral/pharyngeal cancer (OR for the fifth *vs* the first quintile category = 0.59, 95% CI: 0.49–0.71; *P* for trend <0.001) and to laryngeal cancer (OR = 0.67, 95% CI: 0.54–0.83, *P* for trend <0.001). There was, however, appreciable heterogeneity of the estimated effect across studies for oral/pharyngeal cancer. Inverse associations were generally observed for the anatomical subsites of oral and pharyngeal cancer and within covariate strata for both sites.

Conclusion: Our findings suggest that greater vitamin E intake from foods may lower HNC risk, although we were not able to explain the heterogeneity observed across studies or rule out certain sources of bias.

Since the mid 1980s, evidence had been accumulating from laboratory and epidemiological studies on a putative role of antioxidant nutrients, especially β-carotene and vitamin E, in the prevention of cancer of the oral cavity (Garewal, 1995) and cancers at other sites, in general (Chen *et al*, 1988; Block, 1992; Flagg *et al*, 1995; Schorah, 1995; Byers and Guerrero, 1995). In the absence of apparent indications of toxicity, these nutrients provided the possibility to be used widely without close medical supervision and were then the target for specific chemopreventive intervention trials, alone or in combination, to take advantage of possible synergies between them (Shklar and Schwartz, 1993). However, the results from these experiments were not in line with previous knowledge and expectations for several reasons (Bardia *et al*, 2008; Baumeister *et al*, 2009; Bjelakovic *et al*, 2012).

Besides these aspects, traditional single-nutrient analyses and more recent complementary ones on dietary patterns or total antioxidant capacity support the hypothesis that protection against cancer risk may derive from consumption in complex mixtures with other nutrients and bioactive compounds, as found in the matrix provided by whole foods or from combinations of foods (Edefonti *et al*, 2010a,b; Bravi *et al*, 2012; La Vecchia *et al*, 2013). This aspect may be particularly important for vitamin E intake, as this nutrient derives mainly from vegetables and oils of different origin, including olive oil.

The International Head and Neck Cancer Epidemiology (INHANCE) consortium (Hashibe *et al*, 2007; Conway *et al*, 2009; http://www.inhance.utah.edu, last accessed 15 March 2015) was established in 2004 to elucidate the aetiology of head and neck cancers (HNCs) through pooled analyses of individual-level data on HNCs on a large scale. Dietary habits have been previously investigated within the consortium. Among relevant foods and food groups, an inverse association with HNC risk was found for higher intakes of selected vegetables and seafood (Chuang *et al*, 2012). Another analysis focussing on dietary patterns found that a diet rich in monounsaturated, polyunsaturated and saturated fatty acids and vitamin E was inversely associated with oral and pharyngeal cancer and positively associated with laryngeal cancer (Edefonti *et al*, 2012). Results on vitamin E supplementation pointed to a weak and inconsistent inverse association of HNC risk with ever use and increased duration of use, although the oral cavity subsite showed a stronger association with supplemental vitamin E intake. Moreover, the highest frequency category of consumption of vitamin E supplements was associated with a small increase in risk of HNC (Li *et al*, 2012). These inconsistencies in the results to date demonstrate the need for extra research within the consortium on the effective contribution of vitamin E intake from natural sources to HNC risk. Moreover, the INHANCE consortium offers the unique opportunity to clarify: (1) the independent role of vitamin E, after the adjustment for other nutrients previously associated with HNC in independent single-nutrient analyses within the consortium (Edefonti *et al*, 2014; Leoncini *et al*, 2015); and (2) the combined contribution of the intakes of vitamin E and these nutrients, using standard approaches to model the effect of interactions between nutrients on HNC risk.

The specific goals of this analysis were: (1) to describe and account for central tendency and variation in the intakes of vitamin E from natural sources for the populations under examination; (2) to investigate the association between vitamin E intake and the risks of two HNC outcomes – oral and pharyngeal cancers combined and laryngeal cancer – after adjusting for several dietary and nondietary factors; (3) to explore whether effect estimates differ by cancer subsites or in subgroups of subjects, with particular attention to nonsmokers/nondrinkers of alcohol-containing beverages; (4) to explore the potential interaction effect between the intakes of vitamin E and other selected factors – putatively associated with HNC and to our main exposure (other selected nutrients, total fruit and vegetables, supplemental use of vitamin E) – on the two HNC outcomes of interest.

MATERIALS AND METHODS

Design and participants. Within the version 1.5 of the INHANCE consortium pooled data set, 10 case–control studies provided information on vitamin E intake derived from natural sources at the individual level (Blot *et al*, 1988; Schantz *et al*, 1997; Levi *et al*, 1998; Bosetti *et al*, 2003; Peters *et al*, 2005; Cui *et al*, 2006; Suzuki *et al*, 2006; Jayaprakash *et al*, 2006; Divaris *et al*, 2010; Bravi *et al*, 2013). Details on the individual studies, harmonisation of questionnaire data and data pooling methods for the consortium have been previously described (Galeone *et al*, 2014; Edefonti *et al*, 2014) and are reported in the Supplementary Table 1. Briefly, three of the selected studies were from Europe, six were from the United States and one from Asia. Six were hospital-based and four were population-based investigations. Study-specific questionnaires included a Food-Frequency Questionnaire (FFQ) section to assess each subject's usual diet during a reference period preceding cancer diagnosis for cases, or interview date for controls (for details on reproducibility and validity of the study-specific FFQs, see Edefonti *et al*, 2014). Overall, number and wording of FFQ questions were sufficiently detailed to allow for the calculation of intakes of total energy and several nutrients (U.S. Department of Health and Human Services, National Center for Health Statistics, 1982; DietSys, 1999; Applied Research Program, National Cancer Institute, 2005) through study-specific food composition databases (Dresser, 1983; Salvini *et al*, 1998; Resource Council, Science and Technology Agency, the Government of Japan, 2000; Gnagnarella *et al*, 2008; U.S. Department of Agriculture, Agricultural Research Service, 1993, 2013).

Informed consent was obtained from study subjects. The investigations were approved by the relevant institutional review boards, according to the rules adopted in each country.

Selection of subjects. Cases were included if their tumour had been classified by the original study as an invasive tumour of oral

cavity, oropharynx, hypopharynx, oral cavity or pharynx not otherwise specified, larynx or HNC unspecified, according to the International Classification of Diseases for Oncology, 2nd edition (ICD-O-2) or the International Classification of Diseases, 9th or 10th. Subjects with cancers of the salivary glands (ICD-O-2 codes C07-C08) or of the nasal cavity/ear/paranasal sinuses (ICD-O-2 codes C30-C31) were excluded. The ICD coding used for the classification into subsites has been specified in detail previously (Hashibe *et al*, 2007).

Subjects with missing information on natural vitamin E intake (1075 subjects from 6 studies) were removed from the original data. Subjects having an implausible (<500 or >5500 kcal) daily nonalcohol energy intake (defined as: total energy intake (kcal) $-100\times$ number of drinks per day, as 1 drink per day $=$ 100 kcal) (343 subjects) or those having missing values (544 subjects) on nonalcohol energy intake were excluded from the analysis. Cases with missing information on the site of origin of their cancer (22 subjects, with 21 belonging to the MSKCC study) were also removed.

Thus, the present analyses included a total of 18 207 subjects, with 5959 HNC cases and 12 248 controls. There was a total of 1385 oral cavity cancer cases, 1653 oropharyngeal and 571 hypopharyngeal cancer cases (2224 pharyngeal cancer cases), 805 unspecified oral cavity/pharynx cases (giving a total of 4414 oral and pharyngeal cancer cases combined) and 1545 laryngeal cancer cases.

Definition of the exposure variable. We carried out preliminary checks on vitamin E definitions, reference periods of intake and measurement units across studies. In all of the studies, vitamin E was expressed as α-tocopherol equivalents = weighted sum of tochopherols and tochotrienols with vitamin activity. We extracted information on its intake from natural sources (i.e., no inclusion of intakes from fortified foods), and we expressed these intakes on a daily basis.

To assess the comparability of daily intakes across studies, we inspected the kernel density estimation plot (Scott, 2005) representing the study-specific empirical distributions of vitamin E intakes. We also compared study-specific summary statistics of vitamin E intakes across studies. As preliminary checks revealed differences across studies, we computed 'nonalcohol energy-adjusted' vitamin E intakes within each study, on both cases and controls, referring to the residual method (Willett and Stampfer, 1986).

Statistical analysis. Participants from all studies were grouped into five categories according to quintiles of 'nonalcohol energy-adjusted' vitamin E intakes calculated on the overall sample. We estimated the odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) of oral and pharyngeal cancer (including oral, oropharyngeal, hypopharyngeal and unspecified oral/pharyngeal cancer), and laryngeal cancer, separately, for each quintile category (compared with the lowest reference one) using unconditional multiple logistic regression models (Hosmer and Lemeshow, 2000). Tests for linear trend were computed for all models scoring the quintiles as numbers from 1 to 5. To adjust for potential confounders, the main analysis included the following set of variables in all the models: age, sex, education, race/ethnicity, study centre, cigarette smoking status, cigarette intensity, cigarette duration, cigar smoking status, pipe smoking status, alcohol drinking intensity and the interaction between cigarette intensity and alcohol drinking intensity (see Table 1 for categories used). For oral and pharyngeal cancer, separate analyses were conducted by anatomical subsite. For both cancers, stratified analyses were conducted by age, sex, education, geographic region, body mass index at time of interview, tobacco smoking, alcohol drinking and study (see Tables 4 and 5 for categories used, Supplementary Figure 1), and heterogeneity between strata was tested via likelihood ratio tests (Hosmer and Lemeshow, 2000).

We further investigated the potential role of other factors putatively associated with HNC and vitamin E intake on the basis of the literature, including several nutrients (saturated fats, monounsaturated fatty acids, polyunsaturated fatty acids, lutein plus xeaxanthin, total carotenoids, β-carotene equivalents, cryptoxanthin, lycopene and vitamin C) (quintile categories of adjusted nutrient intake via the residual method), total fruits and total vegetables (categories of intake based on study-specific quartiles among the controls) and supplement use of vitamin E (never/ever). For each additional covariate, we proposed a sensitivity analysis, where the aim is to explore whether the inclusion of the covariate changes the magnitude of the ORs for vitamin E intake, and an interaction analysis, where the aim is to assess the magnitude of a potential interaction between the additional covariate and vitamin E intake. We therefore fitted models with and without the extra covariate and the product (interaction) terms for that covariate and vitamin E categories; we then tested for the effects of those covariate and interaction effects using likelihood ratio tests. When the P-value for testing the null hypotheses of no interaction was >0.1, we ignored the interaction and reported results from the main-effects model. We also conducted an influence analysis in which each study was excluded one at a time to ensure that the magnitude of the overall estimates were not dependent on any specific study (Deeks *et al*, 2011).

In all the analyses described, when the P-value for heterogeneity between studies was <0.1, we used a mixed-effects modelling approach and replaced in the tables the fixed-effects ORs and CIs with the corresponding mixed-effects ones. We derived those estimates specifying a random intercept-random slope generalised linear mixed model (GLMM) with a logit link function and binomial family (Pinheiro and Bates, 2000).

For both fixed- and mixed-effects models, we adopted a complete-case approach to the analysis. However, as the Japan study did not provide information on education level for any participant (3495 subjects), we defined an extra category of education including all missing values to avoid the exclusion of these subjects from the analysis.

All statistical tests were two sided. Calculations were performed using the open-source statistical computing environment R (R Core Team, 2014), with its libraries 'lme4' (Bates *et al*, 2011) and 'nnet' (Venables and Ripley, 2002), and Stata (Release 13, StataCorp LP, College Station, TX, USA).

RESULTS

Selected characteristics of cases and controls are shown in Table 1 for oral and pharyngeal cancer and for laryngeal cancer, respectively. Over 70% of cases and controls were white. The Italy Multicenter, US Multicenter and North Carolina studies contributed the largest proportion of cases of both cancer types combined. The US Multicenter provided cases of oral and pharyngeal cancer only. Cases were more likely than controls to smoke tobacco and drink alcohol and to use these products more frequently and for a greater number of years.

Table 2 gives selected descriptive statistics on raw values of vitamin E intake across studies and in all the studies combined. Study-specific distributions were all skewed to the right. The identified summary statistics showed very different values across studies. The Italy Multicenter, Switzerland and Milan (2006–2009) were the top three studies in terms of higher values of vitamin E intake, whereas the US Multicenter study provided the lowest values for all the statistics considered.

Table 3 gives separate ORs and the corresponding CIs for oral and pharyngeal combined and laryngeal cancers by quintile categories of vitamin E intake. For oral and pharyngeal cancer, we reported mixed-effects estimates (P-value for heterogeneity

Table 1. Distribution of cases of oral and pharyngeal cancer and laryngeal cancer and controls according to selected variables (International Head and Neck Cancer Epidemiology (INHANCE) consortium)

	Oral and pharyngeal cases	(%)	Controls	(%)	Laryngeal cases	(%)	Controls	(%)
Age (years)								
<40	208	4.7	681	5.6	26	1.7	681	5.6
⩾40 to ⩽44	194	4.4	563	4.6	45	2.9	563	4.6
⩾45 to ⩽49	446	10.1	949	7.7	123	8.0	949	7.7
⩾50 to ⩽54	645	14.6	1731	14.1	188	12.2	1731	14.1
⩾55 to ⩽59	816	18.5	2079	17.0	271	17.5	2079	17.0
⩾60 to ⩽64	713	16.2	2029	16.6	290	18.8	2029	16.6
⩾65 to ⩽69	658	14.9	1931	15.8	279	18.1	1931	15.8
⩾70 to ⩽74	474	10.7	1540	12.6	227	14.7	1540	12.6
⩾75	260	5.9	743	6.1	96	6.2	743	6.1
Missing	0	0.0	2	0.0	0	0.0	2	0.0
χ^2 (*P*-value)[a]	42.0 (<0.001)				66.5 (<0.001)			
Sex								
Female	1187	26.9	3541	28.9	244	15.8	3541	28.9
Male	3223	73.0	8702	71.0	1300	84.1	8702	71.0
Missing	4	0.1	5	0.0	1	0.1	5	0.0
χ^2 (*P*-value)[a]	6.3 (0.012)				117.8 (<0.001)			
Race								
Black	387	8.8	535	4.4	116	7.5	535	4.4
Others (with Asians)	463	10.5	3089	25.2	101	6.5	3089	25.2
White (with Hispanics)	3555	80.5	8596	70.2	1324	85.7	8596	70.2
Missing	9	0.2	28	0.2	4	0.3	28	0.2
χ^2 (*P*-value)[a]	491.5 (<0.001)				281.7 (<0.001)			
Study name								
Boston	313	7.1	611	5.0	71	4.6	611	5.0
Buffalo	396	9.0	1190	9.7	168	10.9	1190	9.7
Italy Multicenter								
Milan	169	3.8	621	5.1	24	1.6	621	5.1
Pordenone	471	10.7	1528	12.5	409	26.5	1528	12.5
Latina	95	2.2	425	3.5	0	0.0	425	3.5
Japan (2001–2005)	407	9.2	3002	24.5	86	5.6	3002	24.5
Los Angeles	246	5.6	828	6.8	60	3.9	828	6.8
Milan (2006–2009)	131	3.0	691	5.6	200	12.9	691	5.6
MSKCC	74	1.7	123	1.0	32	2.1	123	1.0
North Carolina (2002–2006)	687	15.6	1120	9.1	374	24.2	1120	9.1
Switzerland	367	8.3	877	7.2	121	7.8	877	7.2
US Multicenter								
Atlanta	129	2.9	134	1.1	0	0.0	134	1.1
New Jersey	467	10.6	459	3.7	0	0.0	459	3.7
Los Angeles	398	9.0	501	4.1	0	0.0	501	4.1
San Francisco	64	1.4	138	1.1	0	0.0	138	1.1
χ^2 (*P*-value)[a]	1121.5 (<0.001)				1092.0 (<0.001)			
Education								
⩽Junior high school	863	19.6	2723	22.2	603	39.0	2723	22.2
Some high school	885	20.0	1240	10.1	258	16.7	1240	10.1
High school graduate	588	13.3	1267	10.3	237	15.3	1267	10.3
Technical school, some college	1174	26.6	2305	18.8	214	13.9	2305	18.8
⩾College graduate	491	11.1	1703	13.9	145	9.4	1703	13.9
Missing	413	9.4	3010	24.6	88	5.7	3010	24.6
χ^2 (*P*-value)[a]	766.2 (<0.001)				503.7 (<0.001)			
Cigarette smoking status								
Never	806	18.3	4868	39.7	90	5.8	4868	39.7
Former	1387	31.4	4330	35.4	707	45.8	4330	35.4
Current	2210	50.1	2986	24.4	735	47.6	2986	24.4
Missing	11	0.2	64	0.5	13	0.8	64	0.5
χ^2 (*P*-value)[a]	1139.6 (<0.001)				755.3 (<0.001)			
Cigarette intensity (cigarettes per day)								
Never smoker	806	18.3	4868	39.7	91	5.9	4868	39.7
>0 to ⩽10	471	10.7	1949	15.9	149	9.6	1949	15.9
>10 to ⩽20	1466	33.2	3169	25.9	628	40.6	3169	25.9
>20	1633	37.0	2137	17.4	661	42.8	2137	17.4
Missing	38	0.9	125	1.0	16	1.0	125	1.0
χ^2 (*P*-value)[a]	1111.2 (<0.001)				1015.8 (<0.001)			

Table 1. (Continued)

	Oral and pharyngeal cases	(%)	Controls	(%)	Laryngeal cases	(%)	Controls	(%)
Duration of cigarette smoking (years)								
Never smoker	806	18.3	4868	39.7	91	5.9	4868	39.7
>0 to ⩽20	443	10.0	2166	17.7	102	6.6	2166	17.7
>20	3132	71.0	5123	41.8	1343	86.9	5123	41.8
Missing	33	0.7	91	0.7	9	0.6	91	0.7
χ^2 (*P*-value)[a]	1116.8 (<0.001)				1133.7 (<0.001)			
Cigar smoking								
Never cigar user	3583	81.2	8545	69.8	1323	85.6	8545	69.8
Ever smoked ⩾100 cigars in a lifetime	394	8.9	636	5.2	118	7.6	636	5.2
Missing	437	9.9	3067	25.0	104	6.7	3067	25.0
χ^2 (*P*-value)[a]	33.7 (0.008)				2.8 (0.093)			
Pipe smoking								
Never pipe user	3579	81.1	8327	68.0	1325	85.8	8327	68.0
Ever smoked ⩾100 pipes in a lifetime	399	9.0	864	7.1	115	7.4	864	7.1
Missing	436	9.9	3057	25.0	105	6.8	3057	25.0
χ^2 (*P*-value)[a]	1.2 (0.027)				2.8 (0.094)			
Alcohol consumption (drinks per day)								
Never drinker	548	12.4	3156	25.8	187	12.1	3156	25.8
<1	1030	23.3	4022	32.8	250	16.2	4022	32.8
⩾1 to 3	973	22.0	2934	24.0	344	22.3	2934	24.0
⩾3 to 5	647	14.7	1215	9.9	250	16.2	1215	9.9
⩾5	1216	27.5	921	7.5	514	33.3	921	7.5
χ^2 (*P*-value)[a]	1442.0 (<0.001)				1155.2 (<0.001)			

Abbreviation: MSKCC = Memorial Sloan Kettering Cancer Center.
[a]Missing values were not considered in the calculation of the χ^2 test.

Table 2. Descriptive statistics on raw values of vitamin E intake (mg per day) across studies and in all the studies combined (International Head and Neck Cancer Epidemiology (INHANCE) consortium)

Study name	20%	Median	Mean	80%
Boston	5.37	7.91	9.00	11.58
Buffalo	4.47	6.90	7.78	10.45
Italy Multicenter	10.16	14.08	15.17	19.31
Japan (2001–2005)	6.08	7.42	7.77	9.26
Los Angeles	4.46	6.50	7.51	9.42
Milan (2006–2009)	8.85	11.98	12.76	16.41
MSKCC	5.05	7.22	8.84	11.34
North Carolina (2002–2006)	4.95	7.29	8.04	10.64
Switzerland	9.73	12.90	13.49	16.84
US Multicenter	3.43	4.60	4.88	6.21
All studies combined	5.37	8.30	9.73	13.48

Abbreviation: MSKCC = Memorial Sloan Kettering Cancer Center.

between studies = 0.011), whereas for laryngeal cancer we reported the fixed-effects ones (*P*-value for heterogeneity between studies = 0.464). Vitamin E intake was inversely related to oral and pharyngeal cancer, with an OR of 0.59 (95% CI: 0.49–0.71) for the fifth quintile compared with the first one (*P*-value for trend <0.001). Similarly, the OR for laryngeal cancer was 0.67 (95% CI: 0.54–0.83) for the highest quintile category, with a *P*-value for trend <0.001.

Decreasing ORs with higher intakes of vitamin E were observed across oral and pharyngeal cancer subsites: OR = 0.48 (95% CI: 0.34–0.66) for oral cavity, OR = 0.63 (95% CI: 0.53–0.75) for oropharynx and hypopharynx combined and OR = 0.57 (95% CI: 0.41–0.78) for oral cavity or pharynx not otherwise specified (Supplementary Table 2). The ORs for the oropharynx were similar to those of the hypopharynx site (for instance, for the fifth *vs* the first quintile category, OR = 0.66, 95% CI: 0.60–0.80 and OR = 0.62, 95% CI: 0.47–0.83, respectively) (data not shown) but, given the limited number of hypopharyngeal cancer cases, we decided to combine the results of these subsites.

Table 4 shows the ORs of oral and pharyngeal cancer in strata of selected variables. No appreciable heterogeneity was detected for vitamin E intake across strata, with consistent inverse associations for the third quintile category onwards for all the examined strata. However, in strata of tobacco consumption, a more marked protective association was evident for current smokers in the second and third quintile categories, as compared with non/ex-smokers (*P*-value for heterogeneity across strata <0.001). An appreciable heterogeneity between studies was found for several strata.

Table 5 shows the ORs of laryngeal cancer in strata of selected variables. No appreciable heterogeneity was found for vitamin E intake across strata. An indication of a stronger protective association was evident in the highest quintile category for subjects living in Europe, as compared with those living in the United States or Asia. No appreciable heterogeneity was found between studies in most of the strata.

In the interaction analyses including one extra nutrient among the selected ones (saturated fats, monounsaturated fatty acids, polyunsaturated fatty acids, lutein plus xeaxanthin, total carotenoids, betacarotene equivalents, cryptoxanthin, lycopene and vitamin C) or total fruits/total vegetables or supplement use of vitamin E, no appreciable interaction effect was found between the additional covariate under examination and natural vitamin E for either cancer site.

In the sensitivity analyses including one extra nutrient at a time, likelihood ratio tests pointed to introduce the extra adjustment in the model for eight out of the nine selected nutrients for oral and

Table 3. Odds ratios (ORs)[a] of oral and pharyngeal combined and laryngeal cancers and corresponding confidence intervals (95% CIs) on vitamin E intake quintile categories (International Head and Neck Cancer Epidemiology (INHANCE) consortium)

	Oral and pharyngeal cases	Controls	OR (95% CI)[b]	$P_{studies}$[c]	Laryngeal cases	Controls	OR (95% CI)[b]	$P_{studies}$[c]
I Quintile	976	1479	1 (Reference)	0.011	315	1479	1 (Reference)	0.464
II Quintile	788	1832	0.79 (0.69–0.90)		280	1832	0.94 (0.76–1.16)	
III Quintile	704	1944	0.65 (0.56–0.74)		248	1944	0.75 (0.60–0.93)	
IV Quintile	707	1922	0.64 (0.55–0.74)		298	1922	0.93 (0.75–1.14)	
V Quintile	719	1819	0.59 (0.49–0.71)		261	1819	0.67 (0.54–0.83)	
$P_{for\ linear\ trend}$			<0.001				<0.001	

[a]Estimated from multiple logistic regression models adjusted for age, sex, education, race/ethnicity, study centre, cigarette smoking status, cigarette intensity, cigarette duration, cigar smoking status, pipe smoking status, alcohol drinking intensity and an interaction term between cigarette intensity and alcohol drinking intensity.
[b]For the oral and pharyngeal cancer, heterogeneity between studies was detected ($P<0.1$) and we reported the mixed-effects estimates derived from the corresponding generalised linear mixed model; for laryngeal cancer, there was no appreciable heterogeneity between studies and we reported the fixed-effects estimates.
[c]P for heterogeneity between studies.

Table 4. Odds ratios (ORs)[a,b] of oral and pharyngeal cancers combined and corresponding confidence intervals (95% CIs) on vitamin E intake quintile categories in strata of selected covariates (International Head and Neck Cancer Epidemiology (INHANCE) consortium)

	II Quintile OR (95% CI)	III Quintile OR (95% CI)	IV Quintile OR (95% CI)	V Quintile OR (95% CI)	$P_{studies}$[c]
Age (years)					
<55	0.74 (0.59–0.93)	0.61 (0.47–0.78)	0.67 (0.53–0.84)	0.67 (0.50–0.90)	0.006
⩾55	0.80 (0.68–0.95)	0.66 (0.56–0.78)	0.61 (0.51–0.75)	0.56 (0.43–0.72)	0.004
P_{strata}[d]	0.739				
Sex					
Female	0.87 (0.66–1.16)	0.61 (0.46–0.81)	0.61 (0.46–0.81)	0.72 (0.53–0.99)	0.007
Male	0.77 (0.66–0.90)	0.67 (0.57–0.80)	0.67 (0.57–0.79)	0.54 (0.43–0.68)	0.109
P_{strata}[d]	0.114				
Education					
⩽High school graduate	0.80 (0.67–0.95)	0.65 (0.52–0.80)	0.66 (0.55–0.79)	0.54 (0.41–0.71)	0.010
⩾Some college	0.74 (0.60–0.91)	0.65 (0.53–0.80)	0.64 (0.52–0.79)	0.68 (0.55–0.85)	0.170
P_{strata}[d]	0.587				
Geographic region[e]					
Europe	0.78 (0.62–0.99)	0.57 (0.44–0.74)	0.68 (0.46–1.01)	0.51 (0.31–0.83)	<0.001
America	0.77 (0.66–0.91)	0.69 (0.58–0.81)	0.63 (0.53–0.74)	0.63 (0.52–0.76)	0.393
Asia	0.66 (0.48–0.92)	0.62 (0.45–0.86)	0.60 (0.43–0.84)	0.47 (0.33–0.65)	NE
P_{strata}[d]	0.322				
Body mass index					
<25 kg m^{-2}	0.76 (0.63–0.93)	0.59 (0.48–0.73)	0.64 (0.53–0.79)	0.55 (0.44–0.69)	0.321
⩾25 kg m^{-2}	0.79 (0.65–0.95)	0.72 (0.57–0.89)	0.68 (0.56–0.83)	0.67 (0.53–0.84)	0.030
P_{strata}[d]	0.434				
Tobacco consumption					
Never user	1.00 (0.75–1.32)	0.77 (0.57–1.04)	0.65 (0.47–0.88)	0.58 (0.42–0.80)	0.697
Former user	0.96 (0.74–1.23)	0.76 (0.59–0.98)	0.72 (0.55–0.94)	0.68 (0.52–0.89)	0.295
Current user	0.62 (0.50–0.76)	0.52 (0.42–0.64)	0.61 (0.50–0.76)	0.58 (0.47–0.72)	0.115
P_{strata}[d]	<0.001				
Alcohol consumption[f]					
Never/light drinker	0.88 (0.72–1.07)	0.71 (0.58–0.88)	0.79 (0.64–0.96)	0.72 (0.57–0.90)	0.225
Moderate drinker	0.70 (0.54–0.90)	0.63 (0.50–0.79)	0.59 (0.47–0.75)	0.58 (0.42–0.78)	0.008
Heavy drinker	0.71 (0.50–1.01)	0.55 (0.38–0.79)	0.47 (0.32–0.69)	0.43 (0.31–0.59)	0.104
P_{strata}[d]	0.414				

Abbreviation: NE = not estimable.
[a]Estimated from multiple logistic regression models adjusted for age, sex, education, race/ethnicity, study centre, cigarette smoking status, cigarette intensity, cigarette duration, cigar smoking status, pipe smoking status, alcohol drinking intensity and an interaction term between cigarette intensity and alcohol drinking intensity, when appropriate.
[b]The I quintile category was considered as the reference one.
[c]P for heterogeneity between studies. When the P-value was <0.1 within strata, we reported mixed-effects estimates derived from the corresponding generalised linear mixed model.
[d]P for heterogeneity across strata. When fixed- and mixed-effects models were estimated for different categories of the same stratification variable, likelihood ratio tests for heterogeneity across strata had to be based on comparable mixed-effects models and therefore we re-fitted one or more mixed-effects models to replace the original fixed-effects ones. We consistently reported the corresponding stratum-specific mixed-effects models instead of the fixed-effects ones.
[e]Europe included Italy Multicenter, Switzerland and Milan (2006–2009) studies. North America included Boston, Buffalo, Los Angeles, Memorial Sloan Kettering Cancer Center (MSKCC), North Carolina (2002–2006), and US Multicenter studies. Asia included Japan study only. As Asia included Japan study only, there was no possibility to assess heterogeneity between studies in the Asia stratum.
[f]The never/light drinker category included never drinkers and subjects who drink <1 drink per day; the moderate drinker category included subjects drinking between 1 (included) and 5 drinks per day; the heavy drinker category included subjects drinking ⩾5 drinks per day.

Table 5. Odds ratios (ORs)[a,b] of laryngeal cancer and corresponding confidence intervals (95% CIs) on vitamin E intake quintile categories in strata of selected covariates (International Head and Neck Cancer Epidemiology (INHANCE) consortium)

	II Quintile OR (95% CI)	III Quintile OR (95% CI)	IV Quintile OR (95% CI)	V Quintile OR (95% CI)	$P_{studies}$[c]
Age (years)					
<55	0.98 (0.66–1.47)	0.66 (0.43–1.01)	0.67 (0.44–1.02)	0.52 (0.33–0.80)	0.739
⩾55	0.94 (0.73–1.22)	0.76 (0.58–0.98)	1.08 (0.84–1.38)	0.77 (0.60–0.99)	0.294
P_{strata}[d]	0.176				
Sex					
Female	0.53 (0.32–0.89)	0.33 (0.14–0.76)	0.52 (0.32–0.86)	0.54 (0.27–1.10)	0.677
Male	1.02 (0.82–1.28)	0.80 (0.64–1.01)	0.96 (0.77–1.20)	0.71 (0.50–0.99)	0.015
P_{strata}[d]	0.114				
Education					
⩽High school graduate	0.88 (0.68–1.13)	0.70 (0.54–0.91)	0.95 (0.74–1.22)	0.63 (0.49–0.81)	0.371
⩾Some college	1.08 (0.70–1.65)	0.77 (0.49–1.19)	0.99 (0.65–1.51)	0.96 (0.62–1.49)	0.737
P_{strata}[d]	0.486				
Geographic region[e]					
Europe	0.93 (0.68–1.26)	0.83 (0.61–1.12)	1.08 (0.80–1.44)	0.61 (0.45–0.82)	0.201
America	1.01 (0.74–1.38)	0.71 (0.52–0.99)	0.97 (0.70–1.35)	0.99 (0.71–1.39)	0.830
Asia	1.13 (0.57–2.25)	1.07 (0.55–2.09)	0.84 (0.39–1.82)	0.86 (0.41–1.83)	NE
P_{strata}[d]	0.087				
Body mass index					
$<25\,kg\,m^{-2}$	1.10 (0.79–1.53)	0.87 (0.61–1.22)	1.08 (0.76–1.53)	0.71 (0.50–1.02)	0.695
$\geqslant 25\,kg\,m^{-2}$	0.89 (0.66–1.19)	0.70 (0.52–0.93)	0.94 (0.71–1.24)	0.72 (0.54–0.96)	0.118
P_{strata}[d]	0.830				
Tobacco consumption					
Never user	1.39 (0.63–3.06)	0.89 (0.37–2.13)	0.57 (0.21–1.52)	0.74 (0.30–1.84)	0.793
Former user	1.00 (0.70–1.44)	0.69 (0.47–1.01)	1.07 (0.75–1.52)	0.73 (0.50–1.06)	0.340
Current user	0.82 (0.63–1.08)	0.76 (0.58–0.99)	0.74 (0.56–0.97)	0.68 (0.51–0.90)	0.929
P_{strata}[d]	0.616				
Alcohol consumption[f]					
Never and light drinker	0.97 (0.68–1.37)	0.65 (0.45–0.95)	1.03 (0.72–1.49)	0.74 (0.50–1.10)	0.223
Moderate drinker	0.92 (0.66–1.29)	0.74 (0.53–1.05)	0.86 (0.61–1.21)	0.78 (0.55–1.11)	0.361
Heavy drinker	1.00 (0.63–1.61)	0.89 (0.56–1.43)	1.17 (0.76–1.82)	0.62 (0.40–0.94)	0.650
P_{strata}[d]	0.732				

Abbreviation: NE = not estimable.

[a]Estimated from multiple logistic regression models adjusted for age, sex, education, race/ethnicity, study centre, cigarette smoking status, cigarette intensity, cigarette duration, cigar smoking status, pipe smoking status, alcohol drinking intensity and an interaction term between cigarette intensity and alcohol drinking intensity, when appropriate.

[b]The I quintile category was considered as the reference one.

[c]*P* for heterogeneity between studies. When the *P*-value was <0.1 within strata, we reported mixed-effects estimates derived from the corresponding generalised linear mixed model.

[d]*P* for heterogeneity across strata. When fixed- and mixed-effects models were estimated for different categories of the same stratification variable, likelihood ratio tests for heterogeneity across strata had to be based on comparable mixed-effects models and therefore we re-fitted one or more mixed-effects models to replace the original fixed-effects ones. We consistently reported the corresponding stratum-specific mixed-effects models instead of the fixed-effects ones.

[e]Europe included Italy Multicenter, Switzerland and Milan (2006–2009) studies. North America included Boston, Buffalo, Los Angeles, Memorial Sloan Kettering Cancer Center (MSKCC), North Carolina (2002–2006), and US Multicenter studies. Asia included Japan study only. As Asia included Japan study only, there was no possibility to assess heterogeneity between studies in the Asia stratum.

[f]The never/light drinker category included never drinkers and subjects who drink <1 drink per day; the moderate drinker category included subjects drinking between 1 (included) and 5 drinks per day; the heavy drinker category included subjects drinking ⩾5 drinks per day.

pharyngeal cancer, and for four of them for laryngeal cancer. In either case, the point estimates were generally in line with the ones from the main analysis, although the ORs tended to be higher (data not shown). Similarly, with the additional adjustment by total fruit or total vegetable intake, the inverse association between vitamin E and either cancer site persisted, although the ORs were higher than before (for oral and pharyngeal cancer: OR = 0.70, 95% CI: 0.58–0.84 for the highest quintile category of vitamin E and adjustment by total fruit intake, OR = 0.67, 95% CI: 0.56–0.80 for the adjustment by total vegetable intake; for laryngeal cancer: OR = 0.80, 95% CI: 0.68–0.94 for the highest quintile category of vitamin E and adjustment by total fruit intake, OR = 0.76, 95% CI: 0.64–0.90 for the adjustment by total vegetable intake) (data not shown). With the additional adjustment by supplemental use of vitamin E intake, the corresponding ORs for natural vitamin E intake were in line with the ones obtained without such an adjustment (for oral and pharyngeal cancer: OR = 0.62, 95% CI: 0.50–0.77 for the highest quintile category of vitamin E intake; for laryngeal cancer: OR = 0.68, 95% CI: 0.56–0.83, *P*-values of the likelihood ratio tests of significance of the interaction effect <0.001) (data not shown).

Supplementary Figure 1 shows the study-specific ORs of oral and pharyngeal combined, and laryngeal cancers and corresponding 95% CIs for the highest quintile category of vitamin E intake as compared with the lowest one. The ORs of oral and pharyngeal cancers combined were below unity in seven studies (significant in four) and above unity in two studies (nonsignificant); the ORs of laryngeal cancer were below unity in five studies (significant in one) and above unity in three studies (nonsignificant). Results from the influence analysis were reassuring, as the exclusion of one study at a time did not materially change the point estimates.

DISCUSSION

The present analysis shows that vitamin E intake was inversely related to oral and pharyngeal and to laryngeal cancer risk. The identified associations were generally similar across oral and pharyngeal cancer subsites and in strata of major confounding and risk factors. However, some heterogeneity between studies was detected for oral and pharyngeal cancer.

The term 'vitamin E' includes eight different forms of tocopherols and tocotrienols produced by plants: α-, β-, γ- and δ-tocopherol and α-, β-, γ- and δ-tocotrienol. These fat-soluble food components are thought to have a primary role in protecting both low-density lipoproteins and polyunsaturated fatty acids in cell membranes from oxidation, thus acting indirectly on damage to DNA and other cellular molecules. Indeed, some of the photosynthesis-derived reactive oxygen species generated by oxidation of these compounds in membranes, if not deactivated, can diffuse into the nucleus and cause mutagenesis (Seidman *et al*, 1999). Moreover, compounds with vitamin E activity appear to scavenge oxygen radicals attacking cell membranes and to terminate free radical chain reactions within cell membranes (Schorah, 1995).

Tobacco use per se increases oxidative stress, and therefore enhances the possibility of cancer-causing mutations, oxidisation of lipids and proteins and alteration of signal transduction pathways that damage cells. In heavy alcohol drinkers, the entire nutritional status may be impaired because of malnutrition, and the deficiencies of vitamins and trace elements may contribute to alcohol-associated carcinogenesis. Moreover, the increased oxidative stress observed during ethanol metabolism leads to an increased requirement for glutathion and α-tocopherol (Poschl and Seitz, 2004; World Cancer Research Fund/American Institute for Cancer Research, 2007). In the current paper, we found an interaction between tobacco consumption and vitamin E intake for oral and pharyngeal cancer, with current smokers experiencing a stronger risk reduction at the lowest vitamin E intakes as compared with former and never smokers. No evidence of effect modification was found for alcohol consumption in either cancer site.

Vitamin E is part of a synergistic biochemical system involving also vitamin C, the carotenoids, glutathione and selenium that is designed to protect structural and functional lipids, proteins and nucleic acids from oxidation (Shklar and Schwartz, 1993). The synergy between these nutrients as found in whole foods, their derivation from the same food sources and/or the beneficial effects of other phytochemical compounds found in fruit and vegetables may account for the apparent effects of each of these nutrients. In addition, these reasons may explain why cancer risk is more strongly associated with total fruit and vegetable consumption than with any particular nutrient (Pavia *et al*, 2006; World Cancer Research Fund/American Institute for Cancer Research, 2007). In our analysis, we investigated the possibility of an interaction effect between vitamin E intake and nine potentially related nutrients and that with total fruit and total vegetable consumption. No interaction was evident for either oral and pharyngeal cancers combined or laryngeal cancer and, even when suggested by the likelihood ratio tests, the inclusion in the models of an adjustment by an extra nutrient or by total fruit/vegetable consumption did not materially modify the key finding of an inverse association between higher natural vitamin E intake and the cancer sites of interest.

Some of the studies included in the present analysis already contributed to separate original reports on vitamin E intake or provided data for original publications on data partially overlapping with them (McLaughlin *et al*, 1988; Gridley *et al*, 1990; Day *et al*, 1993; Negri *et al*, 2000; Bidoli *et al*, 2003; Suzuki *et al*, 2006; Bravi *et al*, 2013). Besides them, we are aware of at least seven papers (Riboli *et al*, 1996; Chainani-Wu, 2002; Lucenteforte *et al*, 2009) that assess the association between vitamin E intake from natural sources and HNC and/or its subsites. Among these, one provided results on oral and pharyngeal cancer (Marshall *et al*, 1992), two on laryngeal cancer (Freudenheim *et al*, 1992; Esteve *et al*, 1996), two papers concerned UADTC and their subsites (De Stefani *et al*, 1999; Wright *et al*, 2007) and two UADTC overall (Zheng *et al*, 1995; Kasum *et al*, 2002), with the evidence spread out over the different HNC subsites. Moreover, the same evidence collected on cancer subsites is generally inconclusive. For oral and pharyngeal cancer, a case–control study from the Western New York area showed a weak but nonsignificant protection for higher vitamin E intakes (Marshall *et al*, 1992), a case–control study from Uruguay showed an increased but nonsignificant risk (De Stefani *et al*, 1999) and the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) trial showed a nonsignificant inverse association in male smokers (Wright *et al*, 2007). For laryngeal cancer, the southwestern European study (Esteve *et al*, 1996) and the ATBC trial (Wright *et al*, 2007) reported that vitamin E was related to a significant reduction in risk, whereas the remaining two studies – from the United States (Freudenheim *et al*, 1992) and Uruguay (De Stefani *et al*, 1999) – found a weak-to-moderate nonsignificant reduction in risk. In addition, in the Iowa Women's Health cohort, an inverse nonsignificant association was found in the original study (Zheng *et al*, 1995) for total vitamin E intake (from both diet and supplements) and cancers of the mouth/pharynx/esophagus combined, but no association was observed in its update for dietary vitamin E intake and UADTC overall (including cancers of the nasopharynx, larynx and stomach) after 14 years of follow-up (Kasum *et al*, 2002).

Concerning vitamin E supplementation, two US case–control studies in the 1990s provided preliminary evidence for an inverse association between vitamin E and oral and pharyngeal cancer (Barone *et al*, 1992; Gridley *et al*, 1992). However, more recent results from a systematic review and meta-analysis (Bardia *et al*, 2008) and subsequent original studies (Bairati *et al*, 2005, 2006; Wright *et al*, 2007) did not provide support for vitamin E supplementation on the reduced risk of HNC.

Serum levels of α-tocopherol were related to oral and/or pharyngeal, and laryngeal cancers in an inconsistent way. The ATBC trial in Finland and two nested case–control studies conducted in Finland and the United States provided opposite inconclusive results for oral and pharyngeal cancer (Knekt *et al*, 1991; Zheng *et al*, 1993; Wright *et al*, 2007). In a case–control study from India, serum levels of α-tocopherol were 25% lower among oral cancer cases than among controls (Krishnamurthy and Jaya, 1986). In Finland, increased serum α-tocopherol concentrations were associated with a lower risk of laryngeal cancer in the ATBC study (Wright *et al*, 2007), but similar findings were nonsignificant in the above-mentioned nested case–control study (Knekt *et al*, 1991). A nested case–control study on Japanese–American men in Hawaii found no difference in the (adjusted) mean serum levels of α-tocopherol among UADTC cases and controls (Nomura *et al*, 1997).

Our analysis has several strengths. The large sample size allowed to examine the association between vitamin E intake and HNC by cancer subsite and within relevant subgroups of the study population with the adequate statistical power. The definition of the outcome variable was accurate and standardised across studies. Similarly, we were able to adequately control for the potential confounding effect of several factors that were harmonised across studies. For tobacco smoking and alcohol drinking – the main risk factors for HNC – we accounted for status, intensity and duration of cigarette smoking, status of cigar and pipe use and intensity of alcohol drinking. We also proposed a sensitivity analysis where we assessed the role of several other nutrients, total fruits, total vegetables and supplemental use of vitamin E in their interaction with vitamin E.

However, there are also a few limitations in our work. This analysis suffers from all the issues inherent to a pooled analysis, including, among others, if it is reasonable to pool the study-specific information on the exposure of interest or not, if some preprocessing/harmonisation of the exposure may help and how to do it, how to clearly identify the potential sources of heterogeneity between studies and which statistical approach is more appropriate for the analysis.

Sources of vitamin E are different across countries. A study based on the same FFQ administered in the Italy Multicenter, Milan (2006–2009), and Switzerland studies showed that vitamin E derived from the following food sources: green salad, spinach/other greens, tomatoes, vegetable soup, 'salad with carrots, cucumbers and peppers', apples/pears, peaches/apricots/prunes, 'pasta/rice with tomato sauce', 'tuna/sardines in oil pack' and 'chicken/turkey, roasted, fried, stewed' (~44.5% cumulative contribution) (Favero *et al*, 1997). In the Japanese 102-item FFQ from which our brief Japanese FFQ was derived, vitamin E was supplied by different foods and condiments, with well-milled rice, mixed salad oil, chicken eggs, mixed vegetable oil, spinach, mayonnaise, pumpkin, safflower oil, margarine and koji miso (soybean paste) being the top 10 sources (~53% cumulative contribution) (Imaeda *et al*, 1999). Similarly, major contributors of vitamin E in the US diet from the second National Health and Nutrition examination survey (1976–1980) included, among 15 aggregate categories, the following foods and condiments: fats and oils, vegetables, meat/poultry/fish, desserts, breakfast cereals, fruit, bread/grain products, dairy products, mixed main dishes and nuts/seeds (~90% cumulative contribution), with a major role for highly fortified foods among single items (Murphy *et al*, 1990).

As compared with food groups, extra imprecision is likely present in the measurement of individual nutrients, because of lack of complete information in the nutrient databases used in their calculation (Willett, 2013). This may result in stronger and more consistent associations for food groups than for the corresponding indexes of nutrient intake.

Stronger associations may be observed for other nutrients than vitamin E because of the challenge of measuring vitamin E intake accurately (Byers and Guerrero, 1995). Vitamin E comes largely from foods enriched with vegetable oils that are more difficult to accurately define and measure than foods such as citrus fruit, from which vitamin C is derived (for instance, cumulative contribution of the top 10 foods contributing mostly to vitamin E: 44.5% *vs* 82% for vitamin C, as to the paper based on the Italy Multicenter-Milan (2006–2009)–Switzerland FFQ (Favero *et al*, 1997)). Moreover, vitamin E levels in foods are influenced by processing and preparation methods.

Results of case–control studies are prone to selection and recall bias, and nondifferential misclassification of individual intake might have also occurred because of random measurement error. In addition, although we adjusted our estimates for major recognised risk factors for HNC, uncontrolled confounding from other dietary and nondietary factors cannot be excluded. Concerning smoking and alcohol consumption, we acknowledge that the adjustment variables we used are likely to suffer from mismeasurement to some extent. Oropharyngeal squamous cell carcinoma has also been linked both epidemiologically and molecularly to human papillomavirus (Allen *et al*, 2010). However, our effect estimates did not materially differ across subsites of oral and pharyngeal cancer.

Because of the many observations, outcomes and subsets that are typically made or addressed in epidemiology, multiple comparisons issue has to be somehow taken into account in reporting results of epidemiological studies (Berry, 2012). In the present study, stratified analyses implied carrying out several tests of significance for oral and pharyngeal cancer and several of them for laryngeal cancer too. If a 0.1 cutoff was considered for a heterogeneity deemed to be significant, adjustment for multiple comparisons is somehow acknowledged, although not formally taken into account through existing solutions.

In conclusion, the present paper indicates a protective role for vitamin E in cancers of the oral cavity and pharynx as well as larynx. Although sources of vitamin E may be different across countries, this may point to a protective role of foods rich in vitamin E, including vegetable oils, vegetables and eggs, on cancers at the mentioned sites.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

MH, MF, CLV, PB and AD designed research; KM, DS, CLV, AO, JPZ, DMW, VJ, KM, ZFZ, HM, FL, VE, CB, KK, MM, SS and GPY conducted research and provided single-study databases; SCC and YAL prepared the pooled data set for the analysis; MP provided advice on nutritional issues; VE performed all statistical analyses; VE and FT performed the meta-analysis; VE wrote the paper and had primary responsibility for final content. All authors read and approved the final manuscript.

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